L Number	Hits	Search Text	DB	Time stamp
8	13	backward near3 elimination near8 regression	USPAT; US-PGPUB; DERWENT	2003/10/23 11:41
9	23	(multivariate near8 regression) same (gene or DNA or nucleic)	USPAT; US-PGPUB; DERWENT	2003/10/23 11:56
10	24	comings-d$.in.	USPAT; US-PGPUB; DERWENT	2003/10/23 11:56
11	11	comings-dav$.in.	USPAT; US-PGPUB; DERWENT	2003/10/23 11:57
12	6	comings-dav$.in. and regression	USPAT; US-PGPUB; DERWENT	2003/10/23 11:57

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     (FILE 'HOME' ENTERED AT 12:04:05 ON 23 OCT 2003)

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 12:04:17 ON 23 OCT 2003
L1           875 S COMINGS D?/AU
L2            56 S L1 AND (REGRESSION OR MULTIVARIATE)
L3            25 DUP REM L2 (31 DUPLICATES REMOVED)

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L3 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:678380 CAPLUS
DOCUMENT NUMBER: 139:192455
TITLE: Methods, kits and statistical analysis for detecting polymorphisms in genes associated with late onset Alzheimer's Disease
INVENTOR(S): **Comings, David E.**; MacMurray, James P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 29 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003162207	A1	20030828	US 2002-319855	20021216

PRIORITY APPLN. INFO.: US 2001-339426P P 20011214
US 2002-413775P P 20020927

AB Polygenic disorders are due to the additive effect of multiple genes interacting with the environment. Because of the small effect size of each gene and considerable genetic heterogeneity, when single genes are examd., the outcome of assocn. and linkage analyses are variable from study to study. Techniques are needed that take these unique characteristics of polygenic disorders into consideration. The present invention discloses that the formation of a polygenic score, consisting of the additive effect of multiple candidate genes, and its assessment using receiver operating characteristic (ROC) plots, provides such a technique. Six genes previously shown to be assocd. with Alzheimer's disease were examd., APOE, ACE, ACP1, ESR1, PNMT and SLC6A4. Genotype anal. was performed to identify polymorphisms within these genes, specifically, the e4 allele (APOE gene), the C>T 22251 polymorphism (ACE gene), the VNTR polymorphism (SLC6A4 gene), the ACP1*A polymorphism (ACP1 gene), the XbaI and PvuII polymorphisms (ESR gene), and the G>A-148 and G>A-353 polymorphisms (PNMT gene). The total fraction of the variance, the area under the ROC plots, and the range of risks were similar for both groups indicating that despite genetic heterogeneity and the small effect size of most genes, consistent risk analyses could be obtained by examg. the additive effect of these multiple genes. The present invention also discloses diagnostic tests for detg. a subject's risk of developing Alzheimer's Disease or specifically Late Onset Alzheimer's Disease.

L3 ANSWER 2 OF 25 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003192205 MEDLINE
DOCUMENT NUMBER: 22597303 PubMed ID: 12712467
TITLE: A multigene test for the risk of sporadic breast carcinoma.
AUTHOR: **Comings David E**; Gade-Andavolu Radhika; Cone Lawrence A; Muhleman Donn; MacMurray James P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, California 91010, USA..
dcomings@earthlink.net
SOURCE: CANCER, (2003 May 1) 97 (9) 2160-70.
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030425
Last Updated on STN: 20030521
Entered Medline: 20030520

AB BACKGROUND: Although the identification of the BRCA1 and BRCA2 genes have

been of great interest, these genes account for less than 5% of all breast carcinoma cases. The remaining cases are sporadic. Reanalysis of a large twin study suggested that genetic factors may play a significant role in sporadic breast and other carcinomas. Sporadic breast carcinoma is polygenically inherited. Multiple genes are likely to have an additive effect, each gene accounting for a fraction of the variance. One factor that may have an impact on the development of hormonally responsive breast tumors is the duration of exposure of the breast to estrogen. Therefore, one of the demographic risk factors for breast carcinoma is an early age of onset of menarche. The current study was based on the hypothesis that genes that play a role in demographic risk factors may be breast carcinoma risk genes in their own right. The authors hypothesized that six genes relevant to the timing of the onset of menarche and related risk factors might be candidate genes for breast carcinoma. These were the leptin gene (LEP), the leptin receptor gene (LEPR), the catechol-0-methyltransferase gene (COMT), the dopamine D(2) receptor gene (DRD2), the estrogen 1 receptor gene (ESR1), and the androgen receptor gene (AR). METHODS: The authors examined 67 women with postmenopausal sporadic breast carcinoma and 145 gender and race-matched controls. RESULTS: Five of these genes accounted for a significant percent of the variance (r(2)) of breast carcinoma. The following r(2) and P values were calculated: LEP: 0.073, P < or = 0.0001; LEPR: 0.064, P < or = 0.0002; COMT: 0.073, P < or = 0.0001; AR: 0.040, P < or = 0.0035; and DRD2: 0.018, P < or = 0.05. When evaluated in a **multivariate regression** analysis, they accounted collectively for 24% of the variance of breast carcinoma (P < or = 0.0001). These genes accounted for 40% of the variance (P < or = 0.00001) in a subset of age-matched cases. Individual gene scores were added to form a breast carcinoma risk score (BCRS) that ranged from 0 to 17. When the BCRS was evaluated in a receiver operator characteristic plot, the area under the curve was 0.80 for the full set and 0.869 for the age-matched set. The relative breast carcinoma risk for the different BCRS scores ranged from 0.10 to 11.9. CONCLUSIONS: These results demonstrate a potentially powerful method of evaluating the additive effect of multiple breast carcinoma risk genes to form a potentially clinically useful assessment of women's risk for sporadic breast carcinoma.

DOI 10.1002/cncr.11340

L3 ANSWER 3 OF 25 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2003120885 MEDLINE
DOCUMENT NUMBER: 22521740 PubMed ID: 12634439
TITLE: Phenylethanolamine N-methyltransferase G-148A genetic variant and weight loss in obese women.
AUTHOR: Peters Warren R; MacMurry James P; Walker Jennifer; Giese Russell J Jr; **Comings David E**
CORPORATE SOURCE: Loma Linda University, Center for Health Promotion, Loma Linda, California 92350, USA.. wpeters@univ.llu.edu
SOURCE: OBESITY RESEARCH, (2003 Mar) 11 (3) 415-9.
Journal code: 9305691. ISSN: 1071-7323.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030314
Last Updated on STN: 20030620
Entered Medline: 20030619

AB OBJECTIVE: To understand the impact of the phenylethanolamine N-methyltransferase (PNMT) G-148A gene and nutritional variables on weight loss in obese women. RESEARCH METHODS AND PROCEDURES: One hundred forty-nine women, ages 45 to 65 with a body mass index of >30 kg/m(2), participated in a 6-month, open-label intervention that included sibutramine (15 mg/d) and a monthly health-education class. Anthropometric measurements, vital signs, food frequency, exercise log,

medication compliance, and psychological and sociological questionnaires were completed each month. Genetic polymorphisms of PNMT were determined. RESULTS: Univariate analysis of G/G, G/A, and A/A genotypes against tertiles of percentage of weight loss were significant at 3 but not at 6 months (Pearson chi(2): $p < 0.006$; homozygous/heterozygosity: $p < 0.002$, $p < 0.253$, and $p < 0.122$, respectively). A **regression** model that included the PNMT genetic variation and certain nutrition and exercise variables demonstrated that only the PNMT gene (beta = 0.360, SE 0.585, and $p = 0.003$) was statistically significant at 6 months, and the total calories (beta = -0.925, SE = 0.004, and $p = 0.009$), fiber intake (beta = 0.621, SE = 0.124, and $p = 0.000$), and PNMT (beta = 0.262, SE = 1.415, and $p = 0.024$) were significant. DISCUSSION: The homozygosity/heterozygosity of the PNMT gene was highly predictive of significant weight loss with sibutramine during the first 3 months, which highlights the need for specific pharmacotherapy. The early weight-loss success of those subjects who were homozygous for PNMT may have motivated and selected those that would make further dietary changes, which then augmented their final weight loss.

L3 ANSWER 4 OF 25 EMBASE
on STN

ACCESSION NUMBER: 2003355125 EMBASE
TITLE: The real problem in association studies.
AUTHOR: **Comings D.E.**
CORPORATE SOURCE: Dr. D.E. Comings, Department of Medical Genetics, 1500 East Duarte Road, Duarte, CA 91010-0269, United States. DCOMINGS@earthlink.net
SOURCE: American Journal of Medical Genetics - Neuropsychiatric Genetics, (1 Jan 2003) 116 B/1 (102).
Refs: 5
ISSN: 0148-7299 CODEN: AJMGEB
COUNTRY: United States
DOCUMENT TYPE: Journal; Letter
FILE SEGMENT: 022 Human Genetics
032 Psychiatry
LANGUAGE: English

L3 ANSWER 5 OF 25 CAPLUS

ACCESSION NUMBER: 2003:73950 CAPLUS
DOCUMENT NUMBER: 138:314986
TITLE: Role of the cholinergic muscarinic 2 receptor (CHRM2) gene in cognition
AUTHOR(S): **Comings, D. E.**; Wu, S.; Rostamkhani, M.; McGue, M.; Lacono, W. G.; Cheng, L. S-C.; MacMurray, J. P.
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA, 91010, USA
SOURCE: Molecular Psychiatry (2003), 8(1), 10-11
CODEN: MOPSFQ; ISSN: 1359-4184
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A polemic. A total of 828 adults was examd. to det. if A .fwdarw. T 1890 polymorphism in the 3'UTR of the CHRM2 gene was assocd. with intelligence quotient. The subjects were the parents of twins from the Minnesota Twin and Family Study, a long-term study of the genetics and environmental factors in substance abuse. All the subjects in the CHRM2 study were of Caucasian ancestry. The genetic variants at the CHRM2 gene might be assocd. with different aspects of cognition. In humans, two variables that correlate with cognitive skills are IQ and years of education. A significant linear increase in IQ across the three genotypes of the CHRM2 gene was obsd. By **regression** anal. the CHRM2 gene accounted for approx. 1% of the variance of the IQ scores and years of education. While the percent of the variance of IQ attributable to the CHRM2 gene of 1% may

seem small, it is very likely that IQ is a true polygenic trait due to the additive effect of many genes, each with a small effect.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 25 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2002368188 MEDLINE
DOCUMENT NUMBER: 22108836 PubMed ID: 12116189
TITLE: Association of the muscarinic cholinergic 2 receptor (CHRM2) gene with major depression in women.
AUTHOR: **Comings David E**; Wu Sujihan; Rostamkhani M; McGue Matt; Iacono William G; MacMurray James P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, California, USA.. dcomings@earthlink.net
SOURCE: AMERICAN JOURNAL OF MEDICAL GENETICS, (2002 Jul 8) 114 (5) 527-9.
Journal code: 7708900. ISSN: 0148-7299.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20020713
Last Updated on STN: 20021002
Entered Medline: 20021001

AB Cholinergic neurons have been implicated in depression and in the disorders of REM sleep in depression. We examined a common A-> T 1890 polymorphism in the 3' UTR of the cholinergic muscarinic receptor 2 (CHRM2) gene. There was a significant increase in the frequency of 11 homozygotes in 126 women with major depression (43.7%) compared to 304 women without major depression (25.7%), P =.001. There was no increase in the frequency of 11 homozygotes in 52 men with depression (26.9%) compared to 278 men without depression (27.7%). **Regression** analysis, scoring subjects with the 11 genotype as 1, and those with other genotypes as 0, showed that in women r(2) =.030, F = 13.37, P =.0003. By contrast, in men r(2) =.00001, F = 0.002, P =.96. These results are consistent with a gender-specific role of the CHRM2 gene in depression in women.

L3 ANSWER 7 OF 25 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001464814 MEDLINE
DOCUMENT NUMBER: 21400985 PubMed ID: 11509018
TITLE: Cholecystokinin (CCK) gene as a possible risk factor for smoking: a replication in two independent samples.
AUTHOR: **Comings D E**; Wu S; Gonzalez N; Iacono W G; McGue M; Peters W W; MacMurray J P
CORPORATE SOURCE: Department of Medical Genetics, Beckman Research Institute, City of Hope, Duarte, CA 91010, USA.
SOURCE: MOLECULAR GENETICS AND METABOLISM, (2001 Aug) 73 (4) 349-53.
Journal code: 9805456. ISSN: 1096-7192.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20011105
Entered Medline: 20011101

AB BACKGROUND: CCK is a satiety neuropeptide. Animal studies have shown that both acute and chronic exposure to nicotine results in weight loss which is associated with an increase in hypothalamic CCK and that CCK antagonists ameliorate symptoms of nicotine withdrawal. A major detriment to smoking cessation, especially in women, is the fear of gaining weight.

These observations suggested that genetic variants in the CCK gene might be a possible risk factor for smoking. METHODS: To test this hypothesis we examined the association of the C-45T promoter polymorphism in the Sp1 binding region of the CCK gene with smoking and BMI in two independent groups of subjects. RESULTS: Group 1 consisted of 191 Caucasian women participating in an obesity study. The T allele was present in 15% of women who had never smoked, 20% of ex-smokers, and 58% of current smokers, P < or = 0.0014. The T allele was present in 26.8% of ever-smokers (ex-smokers + current smokers). There was no association with BMI. Group 2 consisted of 725 parents of twins from the Minnesota Twin and Family Study of substance abuse. Logistic **regression** analysis showed that a diagnosis of nicotine dependence was significantly associated with the T allele (P < or = 0.002) and with gender (males > females) (P < or = 0.001), but not with BMI (P < or = 0.68). The T allele was present in 15.9% of parents who had never smoked and 24.7% of ever-smokers, very similar to the results for group 1. INTERPRETATION: These results are consistent with a role of the CCK gene as a risk factor for smoking.

L3 ANSWER 8 OF 25 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001355845 MEDLINE
DOCUMENT NUMBER: 21229564 PubMed ID: 11331109
TITLE: Stress as a mediating factor in the association between the DRD2 TaqI polymorphism and alcoholism.
AUTHOR: Madrid G A; MacMurray J; Lee J W; Anderson B A; **Comings D E**
CORPORATE SOURCE: School of Public Health, Loma Linda University, 11201 Benton St., Loma Linda, CA 92357, USA.
SOURCE: ALCOHOL, (2001 Feb) 23 (2) 117-22.
Journal code: 8502311. ISSN: 0741-8329.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010625
Last Updated on STN: 20010625
Entered Medline: 20010621

AB Results of earlier studies have shown that rating of prior stress exposure in preadolescent boys influenced the association between DRD2 genotypes and alcoholism risk factors, suggesting that variability in stress exposure, either in patient or control samples, could readily account for at least part of the confusion in DRD2 study outcomes. In order to test the hypothesis that the DRD2 A1 allele is only associated with alcoholism in subjects with elevated stress exposure, we examined the gene-stress interactional model in a sample of males of Mayan descent in the Olancho district of Honduras. Ascertainment was based on an epidemiologic, observational cross-sectional design, and the study was approved by the Institutional Review Board. A total of 309 adult males (age range 18-87 years) were interviewed by a physician or a public health nurse, blood samples were obtained for genetic studies, and participants were administered the short version of the Michigan Alcoholism Screening Test (S-MAST) and the Hispanic Stress Inventory (HSI). Three explanatory models were evaluated. The first model tested the effect of the demographic variables alone as predictors of MAST scores, the second tested the effects of stress and DRD2 genotypes separately, and the third tested the effect of the interaction between stress and the DRD2 genotypes. Neither model 1 nor model 2 yielded significant results; neither MAST scores nor HSI scores were found to be associated with DRD2 genotypes. However, Model 3 was confirmed reflecting a significant (P<.05) interaction between DRD2 genotype and stress score as a predictor of MAST score. Additionally, this difference was found to be largely accounted by the HSI occupational/economic stress score, which had a highly significant (P=.003) interaction with DRD2 genotype as a predictor

of MAST score. This stress score was the only one of four that showed levels of stress as high as HSI scores in a US population. The MAST scores of A2A2 genotype participants were found to be nearly identical in low stress and high stress participants, whereas the MAST scores of A1A2 participants increased modestly with stress (P=.01) and that of A1A1 participants increased markedly with stress (P=.001). These findings support the hypothesis that DRD2 genotype-phenotype associations depend on the magnitude of stress exposure, and they lend support to the view that variability in DRD2 study outcomes may in part be explained by this gene-environment interaction.

L3 ANSWER 9 OF 25 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001512454 MEDLINE
DOCUMENT NUMBER: 21437287 PubMed ID: 11553044
TITLE: The additive effect of neurotransmitter genes in pathological gambling.
AUTHOR: **Comings D E**; Gade-Andavolu R; Gonzalez N; Wu S; Muhleman D; Chen C; Koh P; Farwell K; Blake H; Dietz G; MacMurray J P; Lesieur H R; Rugle L J; Rosenthal R J
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010, USA.. dcomings@coh.org
SOURCE: CLINICAL GENETICS, (2001 Aug) 60 (2) 107-16.
Journal code: 0253664. ISSN: 0009-9163.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010919
Last Updated on STN: 20011015
Entered Medline: 20011011

AB As access to gambling increases there is a corresponding increase in the frequency of addiction to gambling, known as pathological gambling. Studies have shown that a number of different neurotransmitters are affected in pathological gamblers and that genetic factors play a role. Polymorphisms at 31 different genes involved in dopamine, serotonin, norepinephrine, GABA and neurotransmitters were genotyped in 139 pathological gamblers and 139 age, race, and sex-matched controls. **Multivariate regression** analysis was used with the presence or absence of pathological gambling as the dependent variable, and the 31 coded genes as the independent variables. Fifteen genes were included in the **regression** equation. The most significant were the DRD2, DRD4, DAT1, TPH, ADRA2C, NMDA1, and PS1 genes. The r(2) or fraction of the variance was less than 0.02 for most genes. Dopamine, serotonin, and norepinephrine genes contributed approximately equally to the risk for pathological gambling. These results indicate that genes influencing a range of brain functions play an additive role as risk factors for pathological gambling. Multi-gene profiles in specific individuals may be of assistance in choosing the appropriate treatment.

L3 ANSWER 10 OF 25 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2001123842 MEDLINE
DOCUMENT NUMBER: 21021110 PubMed ID: 11140838
TITLE: A **multivariate** analysis of 59 candidate genes in personality traits: the temperament and character inventory.
AUTHOR: **Comings D E**; Gade-Andavolu R; Gonzalez N; Wu S; Muhleman D; Blake H; Mann M B; Dietz G; Saucier G; MacMurray J P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010, USA.
CONTRACT NUMBER: RO1-DA08417 (NIDA)
SOURCE: CLINICAL GENETICS, (2000 Nov) 58 (5) 375-85.
Journal code: 0253664. ISSN: 0009-9163.

PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222

AB Cloninger (Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science 1987: 236: 410-416) proposed three basic personality dimensions for temperament: novelty seeking, harm avoidance, and reward dependence. He suggested that novelty seeking primarily utilized dopamine pathways, harm avoidance utilized serotonin pathways, and reward dependence utilized norepinephrine pathways. Subsequently, one additional temperament dimension (persistence) and three character dimensions (cooperativeness, self-directedness, and self-transcendence) were added to form the temperament and character inventory (TCI). We have utilized a previously described **multivariate** analysis technique (Comings DE, Gade-Andavolu R, Gonzalez N et al. Comparison of the role of dopamine, serotonin, and noradrenergic genes in ADHD, ODD and conduct disorder. **Multivariate regression** analysis of 20 genes. Clin Genet 2000: 57: 178-196; Comings DD, Gade-Andavolu R, Gonzalez N et al. **Multivariate** analysis of associations of 42 genes in ADHD, ODD and conduct disorder. Clin Genet 2000: in press) to examine the relative role of 59 candidate genes in the seven TCI traits and test the hypothesis that specific personality traits were associated with specific genes. While there was some tendency for this to be true, a more important trend was the involvement of different ratios of functionally related groups of genes, and of different genotypes of the same genes, for different traits.

L3 ANSWER 11 OF 25 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2001085143 MEDLINE
DOCUMENT NUMBER: 20557283 PubMed ID: 11105655
TITLE: Reward deficiency syndrome: genetic aspects of behavioral disorders.
AUTHOR: **Comings D E**; Blum K
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010, USA.. dcomings@earthlink.net
SOURCE: PROGRESS IN BRAIN RESEARCH, (2000) 126 325-41. Ref: 152
Journal code: 0376441. ISSN: 0079-6123.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118

AB The dopaminergic and opioidergic reward pathways of the brain are critical for survival since they provide the pleasure drives for eating, love and reproduction; these are called 'natural rewards' and involve the release of dopamine in the nucleus accumbens and frontal lobes. However, the same release of dopamine and production of sensations of pleasure can be produced by 'unnatural rewards' such as alcohol, cocaine, methamphetamine, heroin, nicotine, marijuana, and other drugs, and by compulsive activities such as gambling, eating, and sex, and by risk taking behaviors. Since only a minority of individuals become addicted to these compounds or behaviors, it is reasonable to ask what factors distinguish those who do become addicted from those who do not. It has usually been assumed that these behaviors are entirely voluntary and that environmental factors play the major role; however, since all of these behaviors have a significant genetic component, the presence of one or more variant genes presumably

act as risk factors for these behaviors. Since the primary neurotransmitter of the reward pathway is dopamine, genes for dopamine synthesis, degradation, receptors, and transporters are reasonable candidates. However, serotonin, norepinephrine, GABA, opioid, and cannabinoid neurons all modify dopamine metabolism and dopamine neurons. We have proposed that defects in various combinations of the genes for these neurotransmitters result in a Reward Deficiency Syndrome (RDS) and that such individuals are at risk for abuse of the unnatural rewards. Because of its importance, the gene for the [figure: see text] dopamine D2 receptor was a major candidate gene. Studies in the past decade have shown that in various subject groups the Taq I A1 allele of the DRD2 gene is associated with alcoholism, drug abuse, smoking, obesity, compulsive gambling, and several personality traits. A range of other dopamine, opioid, cannabinoid, norepinephrine, and related genes have since been added to the list. Like other behavioral disorders, these are polygenically inherited and each gene accounts for only a small per cent of the variance. Techniques such as the **Multivariate** Analysis of Associations, which simultaneously examine the contribution of multiple genes, hold promise for understanding the genetic make up of polygenic disorders.

L3 ANSWER 12 OF 25 MEDLINE on STN
ACCESSION NUMBER: 2001448309 MEDLINE
DOCUMENT NUMBER: 21221647 PubMed ID: 11324944
TITLE: The DRD4 gene and the spiritual transcendence scale of the character temperament index.
AUTHOR: **Comings D E**; Gonzales N; Saucier G; Johnson J P; MacMurray J P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, California, USA.. dcomings@coh.org
CONTRACT NUMBER: RO1-DA08417 (NIDA)
SOURCE: PSYCHIATRIC GENETICS, (2000 Dec) 10 (4) 185-9. Journal code: 9106748. ISSN: 0955-8829.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB Two hundred male subjects (81 college students and 119 subjects from an addiction treatment unit) were administered the Temperament and Character Inventory (TCI) and genotyped at the 48 base pair repeat polymorphism of the DRD4 gene. Subjects were divided by genotype into those carrying any < 4 repeat allele, those homozygous for the 4 repeat allele, and those with any > 4 repeat allele. The total MANCOVA of seven TCI summary scores, with age and diagnostic group as covariates, was significant (P < or = 0.001). The largest effect was with self-transcendence (P < or = 0.001). The total MANCOVA for the three self-transcendence subscores was significant (P < or = 0.017), with the spiritual acceptance subscore showing the most effect (P < or = 0.001, power = 0.91). These results suggest the DRD4 gene may play a role in the personality trait of spiritual acceptance. This may be a function of the high concentration of the dopamine D4 receptor in the cortical areas, especially the frontal cortex.

L3 ANSWER 13 OF 25 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2000243019 MEDLINE
DOCUMENT NUMBER: 20243019 PubMed ID: 10782925
TITLE: Comparison of the role of dopamine, serotonin, and noradrenaline genes in ADHD, ODD and conduct disorder: **multivariate r gression** analysis of 20 genes.

AUTHOR: **Comings D E**; Gade-Andavolu R; Gonzalez N; Wu S; Muhleman D; Blake H; Dietz G; Saucier G; MacMurray J P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010, USA.. dcomings@coh.org
CONTRACT NUMBER: RO1-DA08417 (NIDA)
SOURCE: CLINICAL GENETICS, (2000 Mar) 57 (3) 178-96. Journal code: 0253664. ISSN: 0009-9163.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000628

AB The present study is based on the proposal that complex disorders resulting from the effects of multiple genes are best investigated by simultaneously examining multiple candidate genes in the same group of subjects. We have examined the effect of 20 genes for dopamine, serotonin, and noradrenergic metabolism on a quantitative score for attention deficit hyperactivity disorder (ADHD) in 336 unrelated Caucasian subjects. The genotypes of each gene were assigned a score from 0 to 2, based on results from the literature or studies in an independent set of subjects (literature-based scoring), or results based on analysis of variance for the sample (optimized gene scoring). **Multivariate** linear **regression** analysis with backward elimination was used to determine which genes contributed most to the phenotype for both coding methods. For optimized gene scoring, three dopamine genes contributed to 2.3% of the variance, p = 0.052; three serotonin genes contributed to 3%, p = 0.015; and six adrenergic genes contributed to 6.9%, p = 0.0006. For all genes combined, 12 genes contributed to 11.6% of the variance, p = 0.0001. These results indicate that the adrenergic genes play a greater role in ADHD than either the dopaminergic or serotonergic genes combined. The results using literature-based gene scoring were similar. An examination of two additional comorbid phenotypes, conduct disorder and oppositional defiant disorder (ODD), indicated they shared genes with ADHD. For ODD different genotypes of the same genes were often used. These results support the value of the simultaneous examination of multiple candidate genes.

L3 ANSWER 14 OF 25 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2001128062 MEDLINE
DOCUMENT NUMBER: 20399756 PubMed ID: 10945659
TITLE: **Multivariate** analysis of associations of 42 genes in ADHD, ODD and conduct disorder.
AUTHOR: **Comings D E**; Gade-Andavolu R; Gonzalez N; Wu S; Muhleman D; Blake H; Chiu F; Wang E; Farwell K; Darakjy S; Baker R; Dietz G; Saucier G; MacMurray J P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010, USA.. dcomings@coh.org
CONTRACT NUMBER: RO1-DA08417 (NIDA)
SOURCE: CLINICAL GENETICS, (2000 Jul) 58 (1) 31-40. Journal code: 0253664. ISSN: 0009-9163.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301

AB In a previous study (Comings DE et al. Comparison of the role of dopamine, serotonin, and noradrenergic genes in ADHD, ODD and conduct disorder. **Multivariate regression** analysis of 20

genes. Clin Genet 2000: 57: 178-196) we examined the role of 20 dopamine, serotonin and norepinephrine genes in attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD), using a **multivariate** analysis of associations (MAA) technique. We have now brought the total number of genes examined to 42 by adding an additional 22 candidate genes. These results indicate that even with the inclusion of these additional genes the noradrenergic genes still played a greater role in ADHD than any other group. Six other neurotransmitter genes were included in the **regression** equation - cholinergic, nicotinic, alpha 4 receptor (CHNRA4), adenosine A2A receptor (ADOA2A), nitric oxide synthase (NOS3), NMDAR1, GRIN2B, and GABRB3. In contrast to ADHD and ODD, CD preferentially utilized hormone and neuropeptide genes These included CCK, CYP19 (aromatase cytochrome P-450), ESR1, and INS ($p = 0.005$). This is consistent with our prior studies indicating a role of the androgen receptor (AR) gene in a range of externalizing behavors. We propose that the MAA technique, by focusing on the additive effect of multiple genes and on the cummulative effect of functionally related groups of genes, provides a powerful approach to the dissection of the genetic basis of polygenic disorders.

L3 ANSWER 15 OF 25 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000354287 EMBASE
TITLE: Molecular heterosis: A review.
AUTHOR: **Comings D.E.**; MacMurray J.P.
CORPORATE SOURCE: D.E. Comings, Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010, United States
SOURCE: Molecular Genetics and Metabolism, (2000) 71/1-2 (19-31). Refs: 58
ISSN: 1096-7192 CODEN: MGMEFF
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 022 Human Genetics
032 Psychiatry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Molecular heterosis occurs when subjects heterozygous for a specific genetic polymorphism show a significantly greater effect (positive heterosis) or lesser effect (negative heterosis) for a quantitative or dichotomous trait than subjects homozygous for either allele. At a molecular level heterosis appears counterintuitive to the expectation that if the 1 allele of a two-allele polymorphism is associated with a decrease in gene expression, those carrying the 11 genotype should show the greatest effect, 12 heterozygotes should be intermediate, and 22 homozygotes should show the least effect. We review the accumulating evidence that molecular heterosis is common in humans and may occur in up to 50% of all gene associations. A number of examples are reviewed, including those for the following genes: ADRA2C, C3 complement, DRD1, DRD2, DRD3, DRD4, ESR1, HP, HBB, HLA-DR DQ, HTR2A, properdin B, SLC6A4, PNMT, and secretor. Several examples are given in which the heterosis is genderspecific. Three explanations for molecular heterosis are proposed. The first is based on an inverted U-shaped response curve in which either to little or too much gene expression is deleterious, with optimal gene expression occurring in 12 heterozygotes. The second proposes an independent third factor causing a hidden stratification of the sample such that for in one set of subjects 11 homozygosity is associated with the highest phenotype score, while in the other set, 22 homozygosity is associated with the highest phenotype score. The third explanation suggests greater fitness in 12 heterozygotes because they show a broader range of gene expression than 11 or 22 homozygotes. Allele-based linkage techniques usually miss heterotic associations. Because up to 50% of association studies show a heterosis effect, this can significantly diminish the power of family-based linkage and association studies. (C) 2000 Academic Press.

L3 ANSWER 16 OF 25 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 1999414330 MEDLINE
DOCUMENT NUMBER: 99414330 PubMed ID: 10483055
TITLE: Potential role of the estrogen receptor gene (ESR1) in anxiety.
AUTHOR: **Comings D E**; Muhleman D; Johnson P; MacMurray J P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010, USA.
CONTRACT NUMBER: R01-DA08417 (NIDA)
SOURCE: MOLECULAR PSYCHIATRY, (1999 Jul) 4 (4) 374-7.
Journal code: 9607835. ISSN: 1359-4184.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991018

AB In addition to neurotransmitters, hormones, acting through the blood stream, also play a role in behavior. To test the potential contribution of genetic variations in hormone receptors we have examined the association between the alleles of the dinucleotide repeat of the estrogen receptor 1 gene (ESR1) and the nine subscores and total score of the SCL-90 in a group of 179 adult males treated for substance abuse. Based on our prior hypothesis that the length of repeat polymorphisms may play a direct role in gene regulation, the alleles were divided into two groups, short (S) and long (L). ANOVA of the SS, LS, and LL genotypes showed a significant association at alpha </=0.05 for three of the SCL-90 scores: anxiety, phobic anxiety, and total symptoms. Of these the anxiety score remained significant at a Bonferroni corrected alpha of </=0.005. By **regression** analysis, the ESR1 gene accounted for 7% of the variance of the anxiety score (P </= 0.0004). These results are consistent with a role of the ESR1gene in human behavior. Since estrogen levels are much higher in women than men, this could account for the increased frequency of anxiety in women.

L3 ANSWER 17 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1999332171 MEDLINE
DOCUMENT NUMBER: 99332171 PubMed ID: 10402503
TITLE: Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse.
AUTHOR: **Comings D E**; Gonzalez N; Wu S; Gade R; Muhleman D; Saucier G; Johnson P; Verde R; Rosenthal R J; Lesieur H R; Rugle L J; Miller W B; MacMurray J P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, California 91010, USA.
CONTRACT NUMBER: RO1-DA08417 (NIDA)
SOURCE: AMERICAN JOURNAL OF MEDICAL GENETICS, (1999 Aug 20) 88 (4) 358-68.
Journal code: 7708900. ISSN: 0148-7299.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991101

AB Prior studies have reported an association between the presence of the 7 repeat allele of the 48 bp repeat polymorphism of the third cytoplasmic loop of the dopamine D4 receptor gene (DRD4) and novelty seeking

behaviors, attention deficit hyperactivity disorder (ADHD), Tourette syndrome (TS), pathological gambling, and substance abuse. However, other studies have failed to replicate some of these observations. To determine whether we could replicate these associations we genotyped 737 individuals from four different groups of control subjects, and 707 index subjects from four different groups of impulsive, compulsive addictive behaviors including substance abuse, pathological gambling, TS, and ADHD. Chi-square analysis of those carrying the 7 allele versus non-7 allele carriers was not significant for any of the groups using a Bonferroni corrected alpha of.0125. However, chi-square analysis of those carrying any 5 to 8 allele versus noncarriers was significant for pathological gambling (p <.0001), ADHD (p </=.01) and the total index group (p </=.0004). When the comparison included all 7 alleles the results were significant for gamblers (p <.0001), TS (p </=.003), ADHD (p </=.003), and the total group (p </=.0002). There was a significant increase in the frequency of heterozygosity versus homozygosity for all alleles for pathological gamblers (p </=.0031) and the total index group (p </=.0015), suggesting that heterosis played a role. In the substance abuse subjects a quantitative summary variable for the severity of drug dependence, based on the Addiction Severity Index, showed that the scores varied by increasing severity across the following genotypes: 44 </= heterozygotes </= 77 </= 22. Studies of other quantitative traits indicated an important role for the 2 allele and the 22, 24, and 27 genotypes. All studies indicated that the role of the DRD4 gene in impulsive, compulsive, addictive behaviors is more complex than a sole focus on the 7 versus non-7 alleles.

L3 ANSWER 18 OF 25 MEDLINE on STN DUPLICATE 12

ACCESSION NUMBER: 1999265639 MEDLINE
DOCUMENT NUMBER: 99265639 PubMed ID: 10334470
TITLE: Additive effect of three noradrenergic genes (ADRA2a, ADRA2C, DBH) on attention-deficit hyperactivity disorder and learning disabilities in Tourette syndrome subjects.
AUTHOR: **Comings D E**; Gade-Andavolu R; Gonzalez N; Blake H; Wu S; MacMurray J P
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010, USA.
CONTRACT NUMBER: RO1-DA08417 (NIDA)
SOURCE: CLINICAL GENETICS, (1999 Mar) 55 (3) 160-72. Journal code: 0253664. ISSN: 0009-9163.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990712
Last Updated on STN: 19990712
Entered Medline: 19990618

AB Halperin et al. (Halperin JM. Newcorn JH, Koda VH, Pick L, McKay KE, Knott P. Noradrenergic mechanisms in ADHD children with and without reading disabilities: a replication and extension. J Am Acad Child Adolesc Psychiatry 1997: 36: 1688 1696) reported a significant increase in plasma norepinephrine (NE) in attention-deficit hyperactivity disorder (ADHD) children with reading and other cognitive disabilities compared to ADHD children without learning disabilities (LD). We examined the hypothesis that ADHD + LD was associated with NE dysfunction at a molecular genetic level by testing for associations and additive effects between polymorphisms at three noradrenergic genes the adrenergic alpha2A receptor (ADRA2A), adrenergic alpha2C receptor (ADRA2C), and dopamine beta-hydroxylase (DBH) genes. A total of 336 subjects consisting of 274 individuals with Tourette syndrome (TS) and 62 normal controls were genotyped. **Regression** analysis showed a significant correlation between scores for ADHD, a history of LD, and poor grade-school academic

performance that was greatest for the additive effect of all three genes. Combined, these three genes accounted for 3.5% of the variance of the ADHD score (p = 0.0005). There was a significant increase in the number of variant NE genes progressing from subjects without ADHD (A-) or learning disorders (LD-) to A + LD - to A - LD + to A + LD + (p = 0.0017), but no comparable effect for dopamine genes. These data support an association between NE genes and ADHD, especially in ADHD + LD subjects.

L3 ANSWER 19 OF 25 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 1999181077 MEDLINE
DOCUMENT NUMBER: 99181077 PubMed ID: 10081236
TITLE: Dopamine receptor genes are associated with age at first sexual intercourse.
AUTHOR: Miller W B; Pasta D J; MacMurray J; Chiu C; Wu H; **Comings D E**
CORPORATE SOURCE: Transnational Family Research Institute, Sunnyvale, CA 94086, USA.
CONTRACT NUMBER: R01 HD23900 (NICHD)
SOURCE: JOURNAL OF BIOSOCIAL SCIENCE, (1999 Jan) 31 (1) 43-54.
Journal code: 0177346. ISSN: 0021-9320.
Report No.: PIP-140796; POP-00285716.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Population
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990426
Last Updated on STN: 20021101
Entered Medline: 19990415

AB The dopaminergic system in the brain seems to play an important role in the regulation of sexual behaviour. The relationship between genes for the D1, D2 and D4 dopamine receptors and age at first sexual intercourse (AFSI) was examined in a sample of 414 non-Hispanic, European-American men and women. A significant association was observed between a DRD2 allele and AFSI and an even stronger association when the DRD2 allele was interacted with a DRD1 allele. A constrained **regression** model was constructed predicting AFSI using sex and a group of nine psychosocial variables as predictors. Adding the DRD2 and the DRD2-by-DRD1 predictors to this model increased the explained variance by 23 and 55%, respectively. Although these findings suggest a stronger association among males than among females, further research will be necessary to clarify this question, as well as to establish whether the observed association holds in other racial/ethnic groups. The dopaminergic system in the brain appears to play an important role in regulating sexual behavior. Specifically, findings to date suggest a major role for dopaminergic receptors in both the preparatory and consummatory phase of male sexual behavior, while its role in female sexual behavior is less conclusive. Findings also indicate that the D(2) subtype of dopamine receptor plays a key role in the control of male sexual behavior, although a D(1) and D(2) subtype interaction is suggested. The relationship between genes for the D(1), D(2), and D(4) dopamine receptors and age at first sexual intercourse (AFSI) was examined in a sample of 414 non-Hispanic, European-American, middle-class, married men and women in Santa Clara County, California. The men and women were of mean ages 31.6 and 29.6 years, respectively. A significant association was found between the DRD2 allele and AFSI, and an even stronger association when the DRD2 allele was interacted with a DRD1 allele. A constrained **regression** model was constructed predicting AFSI using sex and a group of 9 psychosocial variables as predictors. Adding the DRD2 and the DRD2-by-DRD1 predictors to the model increased the explained variance by 23% and 55%, respectively. While these findings suggest a stronger association among males than among females, further research is needed, as well as to establish whether the observed association holds in other racial/ethnic groups.

L3 ANSWER 20 OF 25 MEDLINE on STN
ACCESSION NUMBER: 1998150777 MEDLINE
DOCUMENT NUMBER: 98150777 PubMed ID: 9491813
TITLE: Correlation of length of VNTR alleles at the X-linked MAOA gene and phenotypic effect in Tourette syndrome and drug abuse.
AUTHOR: Gade R; Muhleman D; Blake H; MacMurray J; Johnson P; Verde R; Saucier G; **Comings D E**
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA, USA.
CONTRACT NUMBER: RO1-DA08417 (NIDA)
SOURCE: MOLECULAR PSYCHIATRY, (1998 Jan) 3 (1) 50-60.
Journal code: 9607835. ISSN: 1359-4184.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980507
Last Updated on STN: 19980507
Entered Medline: 19980427

AB Abnormalities in monoamine oxidase (MAO) levels have been implicated in a wide range of psychiatric disorders. We have examined a VNTR polymorphism at the X-linked MAOA gene to test two hypotheses: (1) Do variants of the MAOA gene play a role in any of the behavioral disorders associated with Tourette syndrome or drug abuse? (2) If so, is there any correlation between the length of the alleles and the phenotypic effect? We examined two independent groups: 375 TS patients, relatives and controls, and 280 substance abusers and controls. The alleles were divided into four groups of increasing size. There was a significant association between the MAOA gene and behavioral phenotypes in both groups, and in both the longest alleles were associated with the greatest phenotypic effect. The strongest effect was for the diagnosis of drug dependence (P=0.00003). The VNTR allele groups were in significant linkage disequilibrium with the Fnu4H1 polymorphism previously shown to be associated with MAO-A activity. While these results are consistent with the possibility that different-sized alleles of the short-repeat polymorphisms themselves may play a role in gene regulation, further studies directly linking these alleles with enzyme levels need to be done.

L3 ANSWER 21 OF 25 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 97260148 MEDLINE
DOCUMENT NUMBER: 97260148 PubMed ID: 9106243
TITLE: Association between the cannabinoid receptor gene (CNR1) and the P300 event-related potential.
AUTHOR: Johnson J P; Muhleman D; MacMurray J; Gade R; Verde R; Ask M; Kelley J; **Comings D E**
CORPORATE SOURCE: Jerry L. Pettis VA Hospital, Loma Linda, CA, USA.
CONTRACT NUMBER: R01-DA08417 (NIDA)
SOURCE: MOLECULAR PSYCHIATRY, (1997 Mar) 2 (2) 169-71.
Journal code: 9607835. ISSN: 1359-4184.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970812
Last Updated on STN: 19980206
Entered Medline: 19970730

AB In our prior study we observed a significant association between homozygosity for the > or = alleles of a microsatellite polymorphism of cannabinoid receptor genes (CNR1) and drug dependence. Decreased amplitude of the P300 wave of evoked related potentials (ERP) has long

been shown to be associated with alcohol and drug dependence. The P300 wave reflects attentional resource allocation and active working memory. Since marijuana intoxication has a potent blocking effect on short-term memory we examined the association between the CNR1 alleles and the P300 wave amplitude at three electrodes in 35 alcohol and drug addicts, by MANOVA. There was a significant decrease in amplitude of the P300 wave for all three electrodes (P = 0.028) that was most marked for the frontal lobes (P = 0.008) in subjects homozygous for the CNR1 > or = 5 repeat alleles. **Multivariate regression** analysis indicated the CNR1 gene contributed to 20% of the variance of the frontal lobe P300 wave amplitude.

L3 ANSWER 22 OF 25 MEDLINE on STN
ACCESSION NUMBER: 97233315 MEDLINE
DOCUMENT NUMBER: 97233315 PubMed ID: 9118359
TITLE: Genetic variants of the human obesity (OB) gene: association with body mass index in young women, psychiatric symptoms, and interaction with the dopamine D2 receptor (DRD2) gene.
AUTHOR: **Comings D E**; Gade R; MacMurray J P; Muhleman D; Peters W R
CORPORATE SOURCE: Department of Medical Genetics, City of Hope National Medical Center, Duarte, CA 91910, USA.
CONTRACT NUMBER: RO1-DA08417 (NIDA)
SOURCE: MOLECULAR PSYCHIATRY, (1996 Sep) 1 (4) 325-35. Journal code: 9607835. ISSN: 1359-4184.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 19970506
Entered Medline: 19970424

AB To examine the possible role of genetic variants of the OB gene in obesity we examined alleles of a dinucleotide repeat polymorphism, D7S1875, close to the gene, in a group of adult, non-Hispanic Caucasians. There was a significant correlation with body mass index (BMI) at age 26-30 years for males and females combined (P = 0.04) and females only (P = 0.028). Because of the frequent association between obesity and psychiatric symptoms all subjects were screened with the Symptom List 90 (SCL-90). There was a significant increase in scores for anxiety (P = 0.0005), depression (P = 0.003), and other behaviors for subjects homozygous for the OB1875 < 208-bp alleles. Analysis of covariance indicated that this was directly related to the OB alleles and not secondary to the presence of obesity. There was a significant association between the BMI at ages 16 to 40 and homozygosity for the OB1875 < 208-bp alleles and/or the presence of the DRD2 Taq A1 allele for males and females combined (P = 0.002 to 0.005), and for females alone (P = 0.0017 to 0.0005). For females alone these two genes accounted for up to 22.8% of the variance of the BMI. These results are consistent with the polygenic inheritance of obesity, the greater involvement of genetic factors in women and younger individuals, and suggest that variants of the OB gene are causally involved not only in human obesity but its associated behavioral disorders.

L3 ANSWER 23 OF 25 MEDLINE on STN DUPLICATE 15
ACCESSION NUMBER: 96090228 MEDLINE
DOCUMENT NUMBER: 96090228 PubMed ID: 7485244
TITLE: Role of genetic factors in depression based on studies of Tourette syndrome and ADHD probands and their relatives.
AUTHOR: **Comings D E**
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, California 91010, USA.

SOURCE: AMERICAN JOURNAL OF MEDICAL GENETICS, (1995 Apr 24) 60 (2) 111-21.
Journal code: 7708900. ISSN: 0148-7299.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951215

AB Tourette syndrome (TS) is a common, neuropsychiatric disorder which has many similarities to attention deficit hyperactivity disorder (ADHD). TS probands have a high frequency of a variety of behavioral disorders including depression. The depression may be due to a pleiotrophic effect of the Gts genes, proband ascertainment bias, or a result of coping with the chronic tics. To distinguish between these hypotheses we examined the responses to 17 Diagnostic Interview Schedule questions to evaluate the 9 DSM-III-R criteria for major depressive episode in 1,080 adults consisting of TS and ADHD probands, their relatives and controls. Using a Bonferonni corrected p there was a significant progressive increase in 16 of 17 depressive symptoms and for a life time history of a major depressive episode in groups with increased genetic loading for Gts genes. Similar trends were seen in the small number of ADHD probands and their relatives. There was also a significant increase for these variables in non-proband TS relatives versus non-TS relatives, indicating the association of depression with Gts genes was not due to ascertainment bias or the inappropriate choice of controls. Multiple linear **regression** analysis indicated that obsessive-compulsive behaviors, sex, ADHD, drug abuse, and age all showed a more significant effect on depressive symptoms than the number of tics. The presence or absence of TS in the relatives had a much greater effect on risk for depression than the presence or absence of an episode of major depression in the proband. These results are consistent with the hypothesis that Gts and ADHD genes play a major role in depression.

L3 ANSWER 24 OF 25 MEDLINE on STN
ACCESSION NUMBER: 95109589 MEDLINE
DOCUMENT NUMBER: 95109589 PubMed ID: 7810580
TITLE: Role of genetic factors in human sexual behavior based on studies of Tourette syndrome and ADHD probands and their relatives.
AUTHOR: **Comings D E**
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, California 91010.
SOURCE: AMERICAN JOURNAL OF MEDICAL GENETICS, (1994 Sep 15) 54 (3) 227-41.
Journal code: 7708900. ISSN: 0148-7299.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950215
Last Updated on STN: 19970203
Entered Medline: 19950201

AB Most significant variations in the expression of human sexuality are considered to be the result of learned behavior or psychological problems. Tourette syndrome (TS) is a common, hereditary tic and disinhibition disorder sometimes associated with compulsive use of obscene words (coprolalia) and previously reported to be occasionally associated with exhibitionism. To further explore the relationship between the Gts genes and sexual behavior, questions concerning a wide range of such behaviors were administered to 1,040 subjects, 14 years of age or older, consisting

of 358 TS probands, 101 non-proband relatives with TS, 359 non-TS first degree relatives, 79 attention deficit hyperactivity disorder (ADHD) probands, 70 unaffected relatives of the ADHD probands, and 73 controls. The behaviors included magnitude of sex drive, sex orientation, exhibitionism, transvestitism, transsexualism, sadism, masochism, pedophilia, fetishism, aversion to being touched, and aversion to sex. While most of these behaviors occurred in a distinct minority of TS subjects, there was a significant positive correlation between each behavior examined and the degree of genetic loading for the Gts gene(s). The nature of these behaviors and their association with TS suggests many are variants of obsessive-compulsive disorder. Studies in animals indicate that changes in serotonin and dopamine play a significant role in the sexual behavior and many lines of evidence are consistent with the hypothesis that TS is due to genetic changes in serotonin and dopamine metabolism. These studies suggest that genetic factors play a much greater role in a wide range of forms of sexual expression than previously thought.

L3 ANSWER 25 OF 25 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 94307108 MEDLINE
DOCUMENT NUMBER: 94307108 PubMed ID: 8033754
TITLE: The dopamine D2 receptor gene: a genetic risk factor in substance abuse.
AUTHOR: **Comings D E**; Muhleman D; Ahn C; Gysin R; Flanagan S D
CORPORATE SOURCE: Department of Medical Genetics, City of Hope Medical Center, Duarte, CA 91010.
CONTRACT NUMBER: MH45908 (NIMH)
SOURCE: DRUG AND ALCOHOL DEPENDENCE, (1994 Feb) 34 (3) 175-80. Journal code: 7513587. ISSN: 0376-8716.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940825
Last Updated on STN: 19980206
Entered Medline: 19940812

AB Drug abuse has grown to epidemic proportions. Dopaminergic reward pathways have frequently been implicated in the etiology of drug addiction. To examine the possible role of genetic variants of the dopamine D2 (DRD2) gene in susceptibility to drug abuse we determined the prevalence of the TaqI A1 variant of the DRD2 gene in 200 white patients hospitalized in the Addiction Treatment Unit of a Veterans Administration Hospital. While the prevalence of the D2A1 allele was not significantly increased over controls, it did increase from 21% in subjects with alcohol abuse only to 32% in subjects with alcohol dependence only, consistent with other studies showing an association with the severity of alcoholism. By contrast, of 104 subjects with a discharge diagnosis of drug and alcohol abuse/dependence, 42.3% carried the D2A1 allele versus 29.0% of the 763 white controls (representing all white controls published to date) ($P = 0.006$). Of those who spent more than $25/week on two or more substances, 56.9% carried the D2A1 allele versus 28.2% of those abusing a single substance ($P < 0.0005$). Multiple logistic **regression** analysis showed a highly significant association between multiple substance abuse based on money spent and the presence of the D2A1 allele ($P = 0.0003$) and age of onset of abuse ($P < 0.0001$). D2A1 carriers exceeded D2A2A2 subjects for a history of being expelled from school for fighting ($P = 0.001$), and of those ever jailed for violent crimes, 53.1% carried the D2A1 allele versus 28.8% of those jailed for non-violent crimes ($P = 0.011$).(ABSTRACT TRUNCATED AT 250 WORDS)